CONTINUOUS MANUFACTURING FOR BIOLOGICS & VACCINES

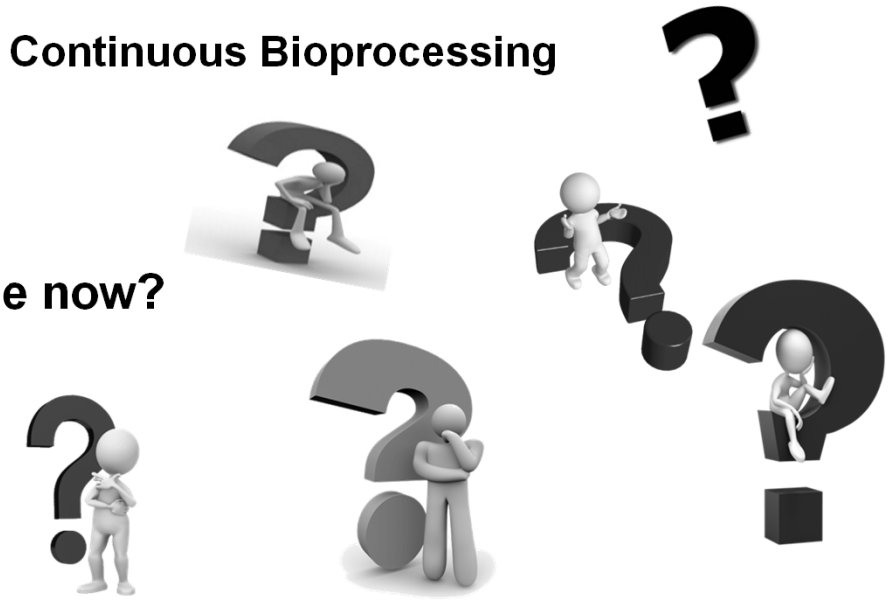
Sue Behrens
ISPE Product Show
Track 2, Session 3
September 26, 2018

Questions about Continuous Bioprocessing

Why?

What's available now?

What's next?



Sue Behrens - Intro

CURRENT

> Sr Director, Process Design
IPS-Integrated Project Services, LLC
- Global EPCMV Capabilities
- Focus on Life Science

> President
SB Executive Consulting, LLC
- Technical / Regulatory Support

PREVIOUS

> **Merck & Co., Inc**
- Manufacturing Support, Operations, Regulatory
- DS: Vaccines, Biologics, Chemical
- DP: Aseptic Filling/Lyo

EDUCATION

> PhD ChE, University of California, Berkeley
> BSChE, University of Michigan, Ann Arbor

ips

Industry Recognized Experts.
Strong Local Execution.

Blue Bell, PA | Chelmsford, MA | Indianapolis, IN | Irvine, CA | Morrisville, NC
Overland Park, KS | San Francisco, CA | Somerset, NJ | Toronto, Canada
São Paulo, Brazil | Birmingham, UK | Dublin, Ireland | Basel, Switzerland | Shanghai, China | Singapore
Mumbai, India | Hyderabad, India | New Delhi, India | Ahmedabad, India

WIB Women In Bio
womeninbio.org
info@womeninbio.org

CONTINUOUS BIOPROCESSING

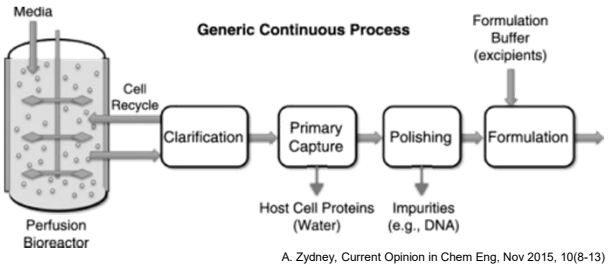
WHY?

Why? Advantages

Quality
> Steady State Operation
> Improved Stability
> Closed Processing
> PAT/Inline Process Control
> Continuous Data Acquisition

Cost
> Reduced scale (capital, footprint)
> Minimize impact of changeovers
> Lower labor utilization
> Minimum inventory

Flexibility
> Steady supply from ongoing production
> Variable scale production



A. Zydney, Current Opinion in Chem Eng, Nov 2015, 10(8-13)

Fully Continuous Process:
Perfusion

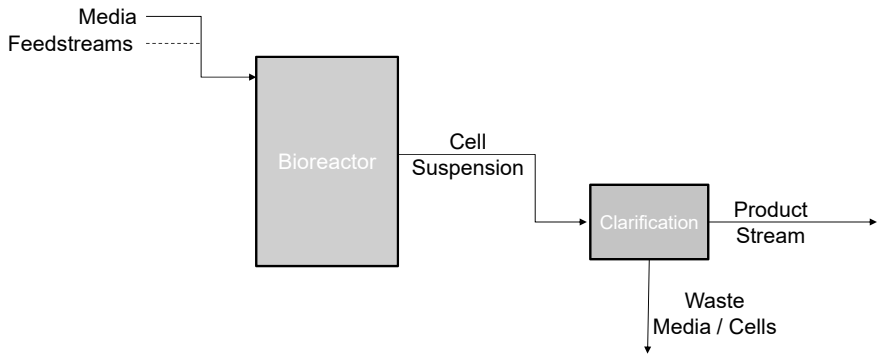
CONTINUOUS USP

WHAT'S AVAILABLE NOW?

Traditional Upstream - Batch / Fed-Batch

Principle:

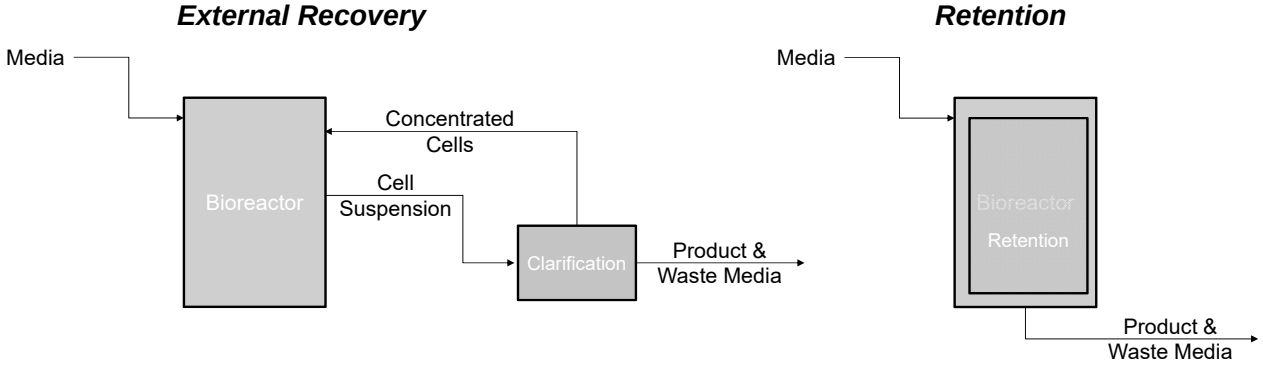
> Inoculate fresh media, cells grow and consume nutrients replacement with fed-batch



Continuous Upstream – What's available now? Perfusion

Principle:

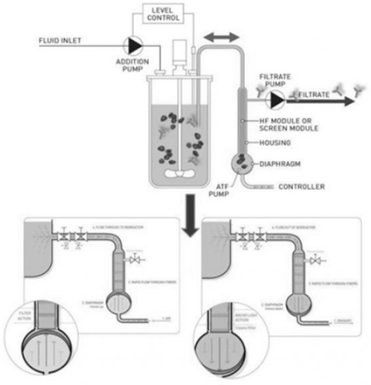
> Recycle cells, provide fresh media, remove waste build-up, recover product



Perfusion with External Filtration What's available now?

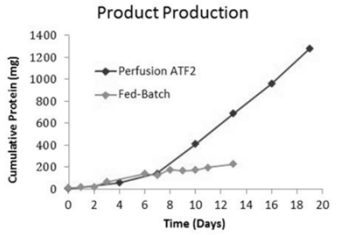
Repligen Xcell™ ATF

> Alternating Tangential Filtration using Hollow Fiber Filter
  – Cell suspension is pulled from the bioreactor
  – Cell-free filtrate is collected through the membrane
  – Cell-containing fluid is returned to the bioreactor
> Alternating Tangential Filtration using Hollow Fiber Filter
> Broadly accepted by industry at multiple locations



BENEFITS

+ Self-cleaning – minimize fouling and extend culture duration
+ Scalable

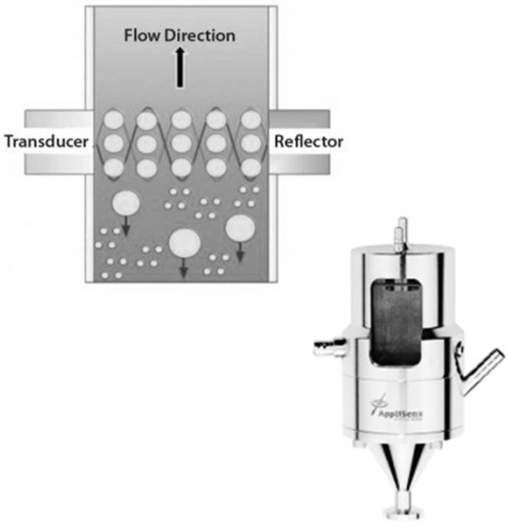


https://www.repligen.com/applications/upstream-applications/perfusion/

Perfusion with Acoustic Wave Separation What's available now?

Pall Cadence Acoustic Separation (CAS)
Applikon BioSep

> High frequency resonant ultrasonic waves
  – Cells held up in the resonance zones
  – Cells clump, settle out by gravity



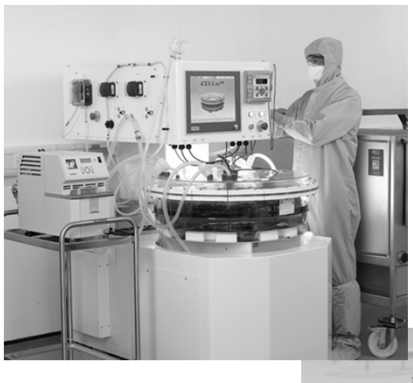
BENEFITS

+ Chamber geometry can be maintained for scale-up
+ Simple mechanism, minimal failure modes
+ Low shear system

Bioreactor Design – Fixed Bed
What's available now?

Pall iCELLis

> Low shear, high surface area
> Porous macrocarrier
> Replaces flask or other adherent systems
> Integrated media distribution system
> In development for vaccines, viral therapy



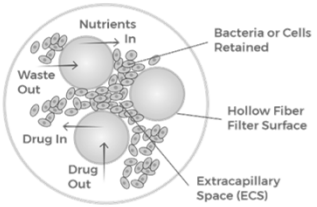
BENEFITS

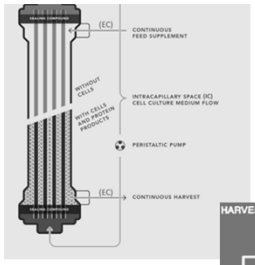
+ Minimum aseptic manipulations
+ Low labor
+ Large scale

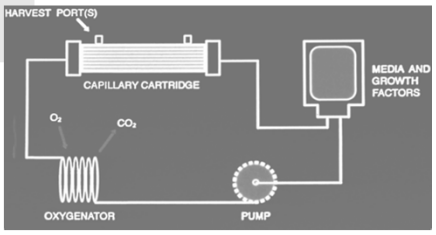
Hollow Fiber Perfusion Bioreactor
What's available now?

Cell Culture Company (C3) AcuSyst®
FiberCell HollowFiber Bioreactor

> Cells grow outside membrane
> Media feed through hollow fiber lumen

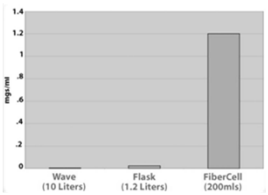






BENEFITS

+ High Cell Density
+ Low volume leads to higher product concentration
+ Low shear system



Continuous Upstream – Additional Operations What's available now?

Perfusion

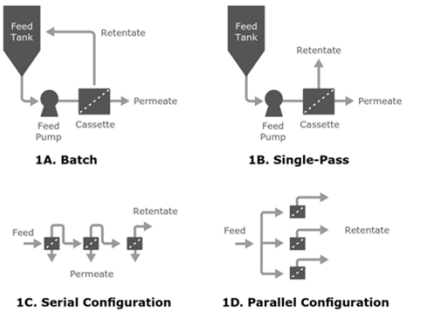
> Centrifugation
> Microcarriers
> Rocker Bioreactors w/ Perfusion membrane

Plug Flow Tubular Bioreactor

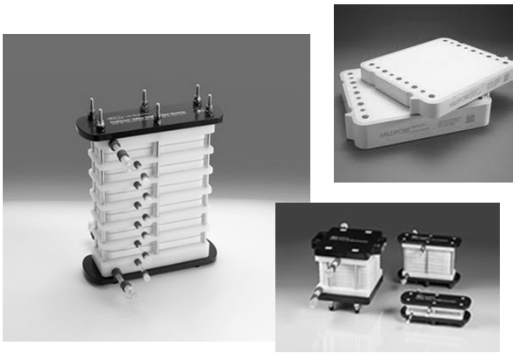
CONTINUOUS DSP

WHAT'S AVAILABLE NOW?

Continuous Filtration What's available now?

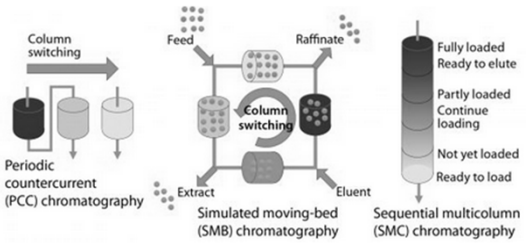


MilliporeSigma Pellicon®
PALL Cadence™ Inline Concentrator, Inline Diafiltration
Single-Pass Tangential Flow Filtration
> Single Pass vs Recirculation
> Multiple stages in series or parallel



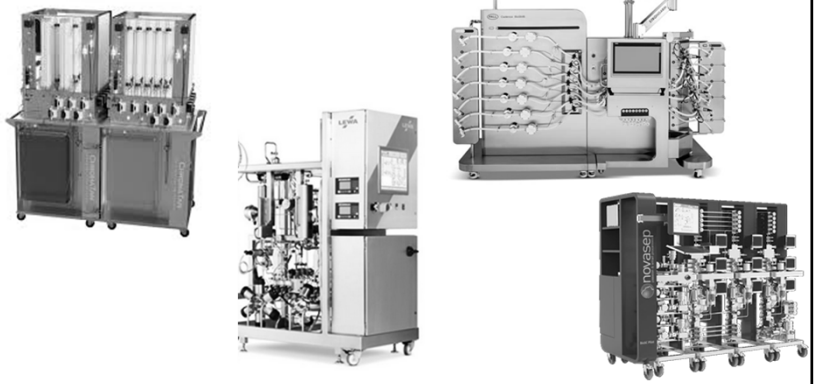
BENEFITS
+ Up to 3-log removal
+ Reduced shear due to elimination of recirculation

Continuous Chromatography What's available now?



Continuous Countercurrent Tangential Chromatography (CCTC)

GE AKTA™, LEWA EcoPrime Twin 100
PALL Cadence BioSMB, Novasep BioSC®, Chromatan
> Multi-cycle, multi-column chromatography
> Enabled through automation of complex fluid management



BENEFITS
+ Lower buffer requirements
+ Fully loaded resin

Continuous Downstream – Additional Operations What's available now?

Filtration

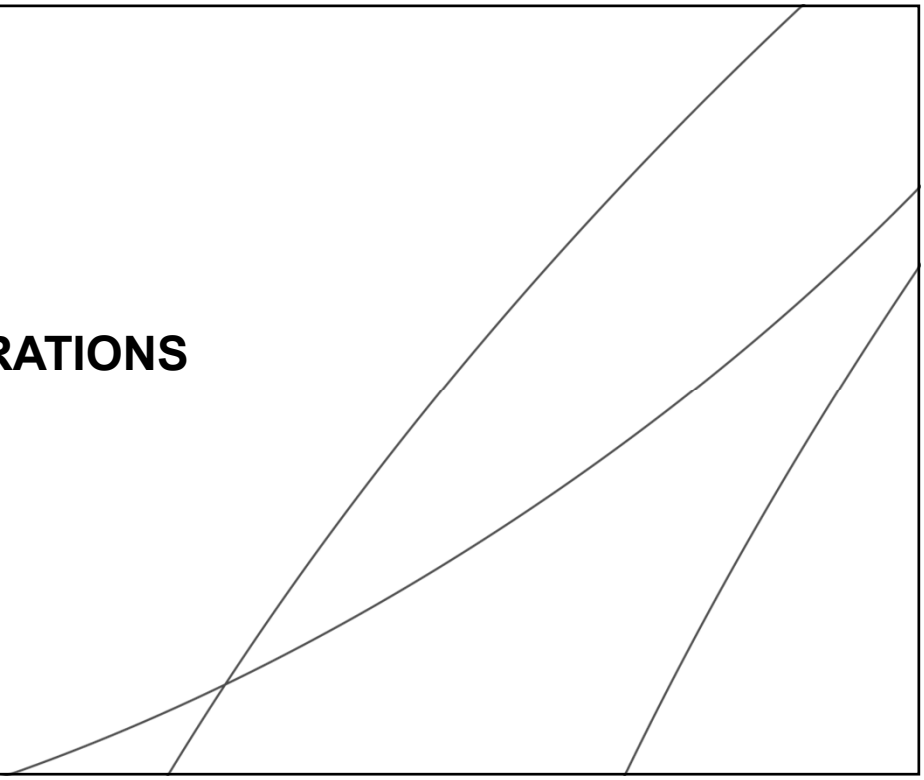
> Microfiltration / Depth Filtration
> Sterile Filtration

Chromatography

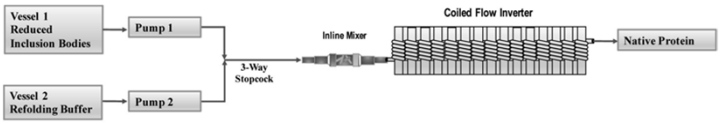
> Membrane Absorbers

CONTINUOUS SUPPORT OPERATIONS

WHAT'S AVAILABLE NOW?



Additional Downstream - What's available now?

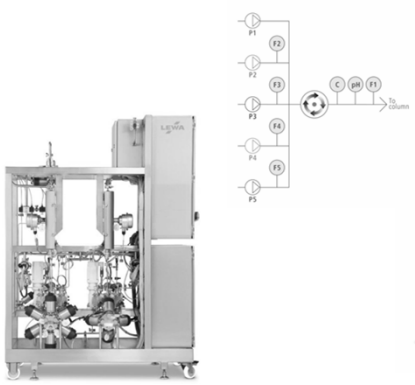


Plug Flow Reactors

> Protein Refolding
> Viral Inactivation

In-Line Buffer Dilution

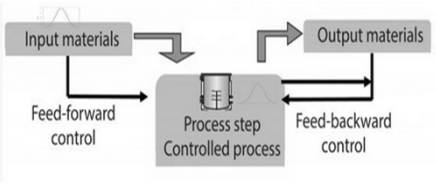
> Online demand for production requirements
> Blend concentrates with water
> Multiple solutions combined for gradient elution
> pH / conductivity control to meet process specifications



PROCESS ANALYTICAL TECHNOLOGY

WHAT'S AVAILABLE NOW?

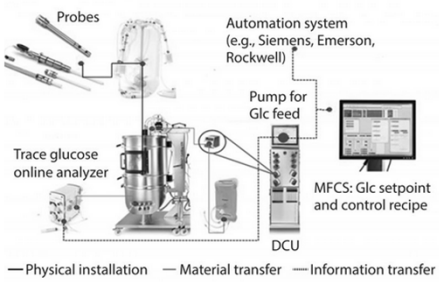
Process Control
What's available now?



Process Analytical Technology

Continuous processing requires robust online analytics and control strategies

> Real-time process monitoring
  – Temperature, pH, DO
  – Off-gas analysis
  – Raman spectroscopy
  – Multiplexed capillary electrophoresis system
> Mechanistic Modelling
> Feedback Control
  – Raw material attributes (UV-HPLC)
  – Sophisticated media-feed strategies



CHALLENGES

WHAT'S NEXT?

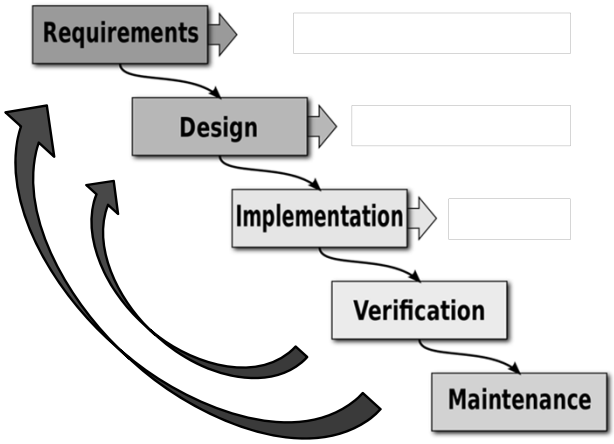
Development Opportunities What's next?

Perfusion
> Dilute product concentration
> Cell line stability can be a risk
> Media volume

Filtration
> Fouling / in-line replacement

Chromatography
> Resin diversity
> Cleaning, re-use

Process control
> Robust in-line monitoring
> Complex control strategy



Challenges for implementation What's next?

> Process Knowledge
  – Need detailed understanding of diverse conditions
  – Understanding impact of deviation
  – Response to Process perturbations
> Operational
  – Broader training for technicians
  – Supply chain management
  – Harmonization of equipment
> Regulatory
  – Complexity of "batch" definition and release strategy
  – Implement for new products with QbD data
  – Transition from legacy manufacturing process

THANK YOU

QUESTIONS ???